

Allergic bronchopulmonary aspergillosis

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INTRODUCTION — Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction, often in patients with asthma or cystic fibrosis (CF), that occurs when bronchi become colonized by *Aspergillus* species [1-4]. Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction can lead to bronchiectasis, fibrosis, and respiratory compromise [5].

The pathophysiology, diagnosis, and treatment of ABPA will be reviewed here. General issues related to bronchiectasis are discussed separately. (See "[Clinical manifestations and diagnosis of bronchiectasis in adults](#)" and "[Treatment of bronchiectasis in adults](#)".)

PATHOPHYSIOLOGY — The pathogenesis of ABPA remains incompletely understood [5,6]. There is no relation between the intensity of exposure to airborne *Aspergillus* spores and rates of sensitization to the fungus as measured by skin testing [7]. Although all spores that are inhaled in sufficient quantities can behave as allergens, the normally low level of IgG against fungal antigens in the circulation and the low anti-fungal secretory IgA in bronchoalveolar fluid suggest that healthy individuals are able to effectively eliminate fungal spores [8,9]. In contrast, exposure of atopic individuals to fungal spores or mycelial fragments results in the formation of IgE and IgG antibodies.

T cells also play an important role in ABPA. There are increases in Th2 CD4+ cell responses to *Aspergillus* antigens both in the bronchoalveolar lymphoid tissue and systemically [5]. *Aspergillus*-responsive T cells generate cytokines interleukin (IL)-4, IL-5, and IL-13, which in turn account for the increases in eosinophilia and IgE in ABPA. In one study, T cell clones specific to the Asp f 1 antigen of *A. fumigatus* were established from the peripheral blood of three patients with ABPA [10]. The majority of these clones were CD4+ cells of the Th2 phenotype, which

produce interleukin (IL)-4 and IL-5 [10]. The response to the Asp f 1 antigen was HLA restricted, being mediated exclusively by either HLA-DR2 or HLA-DR5 and was restricted to specific T cell receptor V-beta chains [10]. In addition, there is increased sensitivity of B cells, T cells, NK cells, and eosinophils to IL-4 [5].

In another study, the costimulatory molecule OX40 ligand was crucial for driving Th2 responses to *A. fumigatus* in the CD4+ cells of patients with CF and ABPA [11]. Heightened Th2 reactivity in these patients correlated with lower mean serum vitamin D levels.

Aspergillus colonization of the asthmatic airway leads to vigorous IgE- and IgG-mediated immune responses superimposed on the asthmatic milieu. In spite of these vigorous responses in ABPA, the fungus is able to colonize the airway and cause recurrent symptoms. Proteolytic enzymes and mycotoxins released by fungi, in concert with Th2-mediated eosinophilic inflammation and IL-8 mediated neutrophilic inflammation [12], may result in airway damage and central bronchiectasis.

Pathology — ABPA is characterized pathologically by mucoid impaction of the bronchi, eosinophilic pneumonia, and bronchocentric granulomatosis in addition to the histologic features of asthma [5,6]. Septated hyphae with acute dichotomous branching may be seen in the mucus-filled bronchial lumen, but fungi do not invade the mucosa. *Aspergillus* is cultured from the sputum in up to two-thirds of patients with ABPA, but hyphae may not be seen by direct microscopy. (See "[Bronchocentric granulomatosis](#)".)

CLINICAL FEATURES — ABPA occurs primarily in patients with asthma (2 to 32 percent of asthma patients) or with CF (1 to 15 percent of CF patients) [5,13]. The clinical picture of ABPA is dominated by asthma complicated by recurrent episodes of bronchial obstruction, fever, malaise, expectoration of brownish mucus plugs, peripheral blood eosinophilia, and at times hemoptysis. Wheezing is not always evident, and some patients present with asymptomatic pulmonary consolidation.

Staging system — In patients with asthma, a staging system for ABPA has been developed to categorize the differing presentations of ABPA ([table 1](#)) [14]. These stages are not necessarily progressive phases of the disease; patients need not inevitably pass from one stage to another.

Radiographic features — The chest radiograph may show parenchymal infiltrates (usually involving the upper lobes), atelectasis due to mucoid impaction, and a number of findings characteristic of bronchiectasis [15] (see "[Clinical manifestations and diagnosis of bronchiectasis in adults](#)"). These include:

- "Tram line" shadows due to thickened walls of nondilated bronchi

- "Parallel lines" due to the presence of ectatic bronchi
- Ring shadows due to mucus-filled bronchi or small abscesses seen en face next to pulmonary blood vessels
- "Toothpaste shadows" due to mucoid impacted second- to fourth-order bronchi
- "Gloved finger shadows" due to intrabronchial exudates with bronchial wall thickening; these appear as branched tubular radiodensities 2 to 3 cm long and 5 to 8 mm wide that extend from the hilus
- Perihilar infiltrates may simulate hilar adenopathy.

High resolution computed tomography — High resolution computed tomography (HRCT) scan of the thorax may show widespread proximal cylindrical bronchiectasis with upper lobe predominance and bronchial wall thickening ([picture 1](#)). However, central bronchiectasis with normal tapering of distal bronchi has not been a consistently sensitive or specific marker for ABPA in all series [[15-20](#)]. In one series of 15 patients, for example, the sensitivity of central bronchiectasis on chest CT as a diagnostic feature for ABPA was only 37 percent [[16](#)]. (See "[High resolution computed tomography of the lungs](#)".)

In addition to bronchiectasis, other findings on HRCT include mucus plugging, high attenuation mucus, atelectasis, peripheral airspace consolidation, or ground-glass attenuation, and possibly mosaic perfusion or air trapping [[17,21](#)]. Using these criteria, in comparison with other forms of eosinophilic lung diseases, radiologists made a correct diagnosis of ABPA in 84 percent of cases [[17](#)]. Coordination between clinical and CT findings are advised to optimize the diagnosis of ABPA [[17](#)].

Pulmonary function testing — Most patients have airflow obstruction and air trapping with reduced FEV1 and increased residual volume; a positive bronchodilator response is found in less than one-half of patients [[22](#)]. Individuals with bronchiectasis or fibrosis may exhibit a mixed obstructive and restrictive pattern. A minority of patients has a reduction in diffusing capacity, an abnormality that may be more common in the presence of bronchiectasis [[22](#)].

DIAGNOSIS — There is no individual test to establish the diagnosis of ABPA [[1,5,6,23](#)]. The major reason for pursuing the diagnosis is that the condition responds to glucocorticoid therapy, and early detection and treatment may reduce the risk of progression to fibrotic disease. The diagnosis is usually confirmed by use of clinical, radiographic, and immunologic criteria.

The major diagnostic features of classic ABPA include:

- A history of asthma

- Immediate skin test reactivity to *Aspergillus* antigens
- Precipitating serum antibodies to *A. fumigatus*
- Serum total IgE concentration >1000 ng/mL
- Peripheral blood eosinophilia >500/mm³
- Lung infiltrates on chest x-ray or chest HRCT
- Central bronchiectasis on chest CT
- Elevated specific serum IgE and IgG to *A. fumigatus*

If the first four criteria above are met but there is no accompanying central bronchiectasis, then a diagnosis of ABPA-S (seropositive) is given.

The minimal essential criteria to diagnose ABPA-CB (central bronchiectasis) are:

- History of asthma
- Immediate skin test reactivity to *A. fumigatus*
- Elevated serum total IgE
- Central bronchiectasis
- Elevated specific serum IgE and IgG to *A. fumigatus*

Evaluation — A skin prick test should be the first step in an asthmatic being evaluated for ABPA. A negative prick skin test followed by negative intradermal reactivity to *Aspergillus* virtually excludes ABPA from consideration.

If the prick test is positive, serum total IgE and precipitins to *Aspergillus* should be assayed. ABPA is excluded if the serum total IgE concentration is less than 1000 ng/mL or if serum precipitins to *Aspergillus* are negative. IgE levels, like levels of blood eosinophilia, may decrease but generally do not normalize if the patient is receiving glucocorticoids.

If the serum total IgE is greater than 1000 ng/mL and the precipitin test is positive for *Aspergillus*, then a presumptive diagnosis of ABPA is made [24]. Determination of specific anti-*Aspergillus fumigatus* IgE and IgG should be performed in such patients: the presence of at least a twofold elevation in specific anti-*Aspergillus* IgE and IgG indices (compared to pooled serum of *Aspergillus*-sensitized non-ABPA asthmatics) indicates seropositive ABPA rather than sensitization to *Aspergillus* in asthmatics without ABPA.

A chest x-ray should be obtained during the initial visit to detect parenchymal infiltrates or bronchiectasis. A negative chest x-ray should be followed by an HRCT scan of the thorax only if a prick skin test and serologic studies are positive. Bronchiectasis by HRCT is present in 15 to 18 percent of non-ABPA asthmatics with positive immediate skin reactivity to *Aspergillus* [18,19,25]. One report compared 17 patients with ABPA with 11 with asthma and a positive skin test to *A. fumigatus* but not other features of ABPA [25]. Bronchiectasis by CT scan was much more common in the patients with ABPA (42 versus 5 percent of lobes).

Although cases have been reported, the diagnosis of ABPA without concurrent asthma must be made with care [26,27]. One series described 11 such patients with ABPA who did not have asthma by history and who had negative bronchodilator responsiveness. Some of these individuals subsequently developed asthma, suggesting that they were diagnosed during a preclinical phase of disease [26]. Three of the 11 patients had hypersensitivity to fungi other than *Aspergillus*, and differences in the host responses to these pathogens may have accounted for the absence of clinical asthma.

ABPA versus conventional asthma — ABPA is frequently raised as a diagnostic possibility in patients with asthma, particularly if immediate skin test reactivity to *Aspergillus* is present. Estimates of the frequency of ABPA among asthmatics vary considerably. As examples, a university tertiary care allergy clinic with special interest in ABPA ultimately diagnosed ABPA in 6 percent of asthmatics with immediate reactivity to *Aspergillus*, but ABPA has been documented in up to 32 percent of patients with asthma and skin test reactivity to *Aspergillus* in other series [13,28-31].

Many asthmatics have one or more findings of ABPA but do not meet full criteria for the diagnosis. The presence of isolated ABPA features may cause diagnostic confusion but does not appear to affect prognosis. Features of ABPA which are found commonly in asthmatics without ABPA include:

- Positive immediate skin reactivity to *A. fumigatus*, which is present in 20 to 30 percent of all asthmatics [29,32]. The label "severe asthma with fungal sensitization" has been increasingly used to describe such patients, as well as those with skin test reactivity to other fungal antigens. As in ABPA, [itraconazole](#) therapy has been demonstrated to be of potential benefit in these patients [33]. (See "[The role of fungi \(molds\) in human disease](#)" and '[Treatment](#)' below.)
- Positive serum precipitins to *Aspergillus*, which occur in 10 percent of asthmatics without ABPA, and in 10 percent of nonasthmatic patients with chronic lung disease [34,35]
- Recurrent mucoid impaction and atelectasis, particularly among poorly controlled asthmatics
- Peripheral blood eosinophilia and elevation of serum total IgE

ABPA in cystic fibrosis — It is difficult to establish the diagnosis of ABPA in patients with cystic fibrosis (CF), but identification and treatment of the disease may result in improvement in symptoms and pulmonary function. The prevalence of ABPA in children with CF appears to be 2 to 15 percent, while adults with CF may

have a lower prevalence [[5,36-42](#)].

A Cystic Fibrosis Foundation Consensus Conference [[5](#)] has identified diagnostic criteria for ABPA in CF:

Classic case:

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology
- Serum total IgE of >2400 ng/mL (unless patient is receiving systemic glucocorticoids - if so retest when patient is off steroids)
- Immediate skin test reactivity to *Aspergillus* or in vitro presence of anti-*Aspergillus* IgE antibodies
- Precipitating antibodies to *A. fumigatus* or serum IgG antibody to *A. fumigatus*
- New or recent abnormalities on chest x-ray (infiltrates or mucus plugging) or chest CT (bronchiectasis) that do not clear with antibiotics and physiotherapy

The minimal diagnostic criteria:

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another etiology
- Total serum IgE >1200 ng/mL (if total IgE is 480 to 1200 ng/mL, repeat testing in one to three months; if the patient is taking steroids, repeat when steroid treatment is discontinued)
- Immediate skin test reactivity to *Aspergillus* or in vitro presence of anti-*Aspergillus* IgE antibodies

Plus one of the following:

- Serum precipitins or IgG antibody to *A. fumigatus*
- New or recent abnormalities on chest x-ray (infiltrates or mucus plugging) or chest CT (bronchiectasis) that does not clear with antibiotics and physiotherapy

CF is complicated by recurrent pulmonary infections, bronchiectasis, and microbial colonization. (See "[Cystic fibrosis: Clinical manifestations of pulmonary disease](#)".) ABPA should be suspected if patients with pulmonary infiltrates or clinical deterioration do not respond to one week of antibiotic treatment. Consensus

Conference guidelines for screening for ABPA in CF include:

- Maintain a high level of suspicion for ABPA in CF patients >6 years of age.
- Determine the total serum IgE concentration annually. If the concentration is >1200 ng/mL, evaluate for anti-Aspergillus IgE by determining skin test reactivity or in vitro testing for IgE to *A. fumigatus*.
- If the serum IgE is 480 to 1200 ng/mL, repeat the measurement if there is increased clinical suspicion of ABPA and perform further diagnostic tests (eg, evaluate skin tests, in vitro tests for anti-Aspergillus fumigatus IgE, IgG and precipitins, chest x-ray).

Treatment with glucocorticoids should be instituted, and therapy should result in a reduction in IgE level. In one retrospective series of 16 patients with CF and ABPA, the use of [itraconazole](#) was associated with a 47 percent reduction in average daily glucocorticoid dose and a 55 percent reduction in the number of acute ABPA episodes [41]. ABPA and other semi-invasive manifestations of Aspergillus infection (eg, bronchial aspergillosis, wound or anastomotic infection) can occur after lung transplantation in CF [43]. (See "[Fungal infections following lung transplantation](#)".)

ABPA and pulmonary eosinophilia — The differential diagnosis of transitory lung infiltrates associated with peripheral blood eosinophilia should always include ABPA, which is the most common cause of this syndrome in Great Britain [44-47]. (See "[Causes of pulmonary eosinophilia](#)".) Such findings should also prompt consideration of other diagnoses, including:

- Acute or chronic eosinophilic pneumonia (see "[Idiopathic acute eosinophilic pneumonia](#)")
- Drug-induced eosinophilic pneumonia
- Churg-Strauss syndrome (see "[Epidemiology, pathogenesis, and pathology of Churg-Strauss syndrome \(allergic granulomatosis and angiitis\)](#)")
- Hypereosinophilic syndromes (see "[Clinical manifestations, pathophysiology, and diagnosis of the hypereosinophilic syndromes](#)")
- Tropical eosinophilic pneumonia (see "[Tropical filarial pulmonary eosinophilia](#)")
- Loeffler's pneumonia (see "[Pulmonary manifestations of ascariasis](#)")
- Autoimmune diseases such as rheumatoid arthritis, pernicious anemia, and sarcoidosis
- Complications of crack-cocaine abuse (see "[Pulmonary complications of](#)")

[cocaine abuse](#)")

A prick test and assay of serum Aspergillus precipitins should be performed if the diagnosis of ABPA is entertained. A negative prick skin test and the absence of precipitins to Aspergillus virtually exclude ABPA.

ABPA and bronchiectasis — Patients with bronchiectasis should be evaluated for ABPA unless the patient has a history suggestive of a prior necrotizing pneumonia. Although central bronchiectasis is often seen in ABPA, it is a nonspecific finding. As an example, one series of 168 patients found that CT characteristics of bronchiectasis failed to differentiate disease caused by ABPA from that due to hypogammaglobulinemia, ciliary dysfunction, CF, or idiopathic causes [16]. The bronchiectasis was more likely to be widespread and central in ABPA than in other causes, but these findings were not predictive in the individual patient.

TREATMENT — Treatment of ABPA aims to control episodes of acute inflammation and to limit progressive lung injury. Glucocorticoids are most commonly used, although there is evidence of benefit from combined therapy with [itraconazole](#).

The 2008 Infectious Diseases Society of America guidelines on the treatment of aspergillosis recommend that therapy of ABPA should consist of a combination of glucocorticoids and [itraconazole](#) [48].

Glucocorticoids — Glucocorticoids are effective for controlling ABPA but are associated with significant immunosuppressive and metabolic side effects [28,45,49,50]. (See "[Major side effects of systemic glucocorticoids](#)".)

The glucocorticoid dose varies with the stage of disease. Inhaled steroids may help control symptoms of asthma but do not have documented efficacy in preventing acute episodes of ABPA. (See '[Staging system](#)' above.)

Although the specific choice of glucocorticoid regimen often varies among clinicians and is tailored to the individual patient, we generally use the following approach:

- An acute flare of ABPA (stage I) is treated with 0.5 to 1.0 mg/kg of [prednisone](#) daily for 14 days followed by conversion to an every other day regimen and a slow taper over three to six months.
- The clinical response to glucocorticoids should be monitored with serial monthly or bimonthly measurement of the serum total IgE concentration [51]. Resolution of radiographic infiltrates and clinical improvement (remission or stage II disease) generally are accompanied by at least a 35 percent reduction in serum total IgE [4]. However, patients with a baseline IgE level <2500 IU/mL may not have as large of a percentage decrease in IgE in response to glucocorticoids [52]. An increase in serum IgE may herald or accompany lung

infiltrates and peripheral eosinophilia [51,53].

- Recurrent exacerbations or flares (stage III) are frequent and are accompanied by at least a 100 percent rise in serum total IgE over baseline. We recommend a tapered glucocorticoid regimen as detailed above for stage I disease. Twenty to 35 percent of flares are asymptomatic and are detected radiographically and serologically. Chest x-rays should be obtained if signs of an asymptomatic flare are detected during physical examination or if a patient has an established pattern of recurrent, asymptomatic flares.
- Stage IV disease (glucocorticoid-dependent asthma) is present when a patient cannot discontinue glucocorticoids without a recrudescence of asthma symptoms.
- Stage II disease (remission) and stage V disease (fibrotic lung disease) do not warrant glucocorticoid treatment.

Antifungal agents — Two randomized trials, a retrospective cohort study, and a small prospective study have demonstrated the utility of [itraconazole](#) in addition to glucocorticoids for the therapy of ABPA [54-58]. The larger of the randomized trials compared itraconazole with placebo in 55 patients already receiving glucocorticoids [54]. The addition of itraconazole for 16 weeks was associated with a significant increase in the likelihood of a clinical response (46 versus 19 percent). A response was defined as a reduction of at least 50 percent in the glucocorticoid dose, a decrease of at least 25 percent in the serum IgE concentration, and one of the following: an improvement of at least 25 percent in exercise tolerance or pulmonary function tests, or partial or complete resolution of pulmonary infiltrates. Adverse effects were similar in both groups. While total IgE decreases with therapy, specific IgE antibodies against *A. fumigatus* may not [58].

[Itraconazole](#) is thought to work by reducing the antigenic stimulus for bronchial inflammation [48]. The antifungal effects can be inferred by the ability of itraconazole to reduce specific *Aspergillus* IgG [56].

Another possible contributor to [itraconazole](#) action in ABPA is by impairing metabolism of the glucocorticoid, thereby raising plasma levels. This effect is best described with [methylprednisolone](#) but may not be important with [prednisolone](#), which is the active form of [prednisone](#) [59,60]. The development of Cushing's syndrome has been recognized in ABPA patients treated with itraconazole and glucocorticoids, with most case reports involving inhaled glucocorticoids [61-63]. Such patients are also at risk for adrenal insufficiency due to inhibition of cortisol synthesis, which becomes apparent with glucocorticoid dose reduction [63-65].

Many clinicians no longer use [itraconazole](#) for invasive forms of pulmonary

aspergillosis and use [voriconazole](#) instead. Successful use of voriconazole in ABPA has also been reported [66,67]. Whether voriconazole is superior to itraconazole in ABPA remains unknown, although voriconazole has distinct advantages to itraconazole such as improved tolerance and bioavailability. There are no data on the efficacy of other newer azole agents such as [posaconazole](#) in ABPA. (See "[Treatment of chronic pulmonary aspergillosis](#)" and "[Treatment of invasive aspergillosis](#)" and "[Pharmacology of azoles](#)".)

Use of nebulized [amphotericin B](#) in patients with ABPA has also been reported [68].

We suggest [itraconazole](#) for 16 weeks in all patients who require substantial doses of glucocorticoids, with the goal of enabling a reduction in the glucocorticoid dose. We also suggest itraconazole in patients with relapsed ABPA.

The oral [itraconazole](#) regimen in adults is 200 mg three times a day for three days followed by 200 mg twice daily with food. Children should receive 5 mg/kg per day given either once a day, or if the total dose exceeds 200 mg/day, given in divided twice daily doses with food. Liver function tests should be monitored monthly for any evidence of itraconazole side effects. (See "[Pharmacology of azoles](#)".)

The liquid formulation of [itraconazole](#), given in the same dosages noted above, overcomes problems caused by poor absorption of the capsule and achieves approximately 30 percent higher concentrations in the serum at the same dose. The solution should be given on an empty stomach to achieve the highest serum concentrations. However, more gastrointestinal upset occurs with the solution formulation, which precludes its use in some patients.

Acid-blocking drugs should be avoided when the capsule formulation is given.

The usual duration of therapy is three to six months [5]. In the two randomized trials that have been performed, the duration was 16 weeks [54,56]. There has been a case report of azole resistance in a patient with ABPA treated with [itraconazole](#) for seven months [69].

Omalizumab — A potential additional therapy that may be beneficial in the treatment of ABPA in children with cystic fibrosis (CF) is [omalizumab](#), a humanized monoclonal antibody against IgE. In case reports, seven children with CF and ABPA who were poorly controlled on glucocorticoids or experiencing ABPA exacerbation were treated with omalizumab (300 to 375 mg subcutaneously every two weeks) [70-73]. In all seven children, respiratory function improved and glucocorticoid administration was able to be terminated in those receiving glucocorticoids. The duration of follow-up in these reports ranged from 11 weeks to 18 months. However, in another case report of a child with CF and ABPA treated with omalizumab, glucocorticoids were not able to be weaned over a 12 month period while the patient was receiving 300 mg every four weeks of the drug [74].

Proof of efficacy of [omalizumab](#) in the treatment of ABPA in those with and without CF await more definitive clinical trials.

PROGNOSIS — The natural history, progression between stages, remission, and recurrences of ABPA are not well understood [24]. The general teaching is that treatment in the earlier stages is important to try to prevent the development of bronchiectasis or pulmonary fibrosis and that stage V disease carries a worse prognosis. However, progression through these stages is assumed and has not been clearly established. There are cases of pulmonary fibrosis in patients with few preceding episodes or symptoms [3].

SUMMARY

- Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction of the airways that occurs when bronchi become colonized by *Aspergillus* species. ABPA may also develop in patients with cystic fibrosis. Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction can lead to bronchiectasis, fibrosis, and respiratory compromise. (See '[Introduction](#)' above.)
- *Aspergillus* colonization of the asthmatic airway leads to vigorous IgE- and IgG-mediated immune responses superimposed on the asthmatic milieu. Proteolytic enzymes and mycotoxins released by fungi, in concert with Th2-mediated eosinophilic inflammation and IL-8 mediated neutrophilic inflammation, may result in airway damage and central bronchiectasis. (See '[Pathophysiology](#)' above.)
- ABPA is characterized pathologically by mucoid impaction of the bronchi, eosinophilic pneumonia, and bronchocentric granulomatosis in addition to the histologic features of asthma. Septated hyphae with acute dichotomous branching may be seen in the mucus-filled bronchial lumen, but fungi do not invade the mucosa. (See '[Pathology](#)' above.)
- The clinical picture of ABPA is dominated by asthma complicated by recurrent episodes of bronchial obstruction, fever, malaise, expectoration of brownish mucus plugs, peripheral blood eosinophilia, and at times hemoptysis. (See '[Clinical features](#)' above.)
- In patients with asthma a staging system for ABPA has been developed to categorize the differing presentations of ABPA ([table 1](#)). (See '[Staging system](#)' above.)
- There is no individual test to establish the diagnosis of ABPA. The diagnosis is usually confirmed by use of clinical, radiographic, and immunologic criteria.

The major diagnostic features of classic ABPA include:

- A history of asthma
- Immediate skin test reactivity to *Aspergillus* antigens
- Precipitating serum antibodies to *A. fumigatus*
- Serum total IgE concentration >1000 ng/mL
- Peripheral blood eosinophilia >500/mm³
- Lung infiltrates on chest x-ray or chest high-resolution CT
- Central bronchiectasis on chest CT
- Elevated specific serum IgE and IgG to *A. fumigatus*

The use of these features for establishing the diagnosis is discussed above.
(See '[Diagnosis](#)' above.)

- A skin prick test should be the first step in an asthmatic being evaluated for ABPA. A negative prick skin test followed by negative intradermal reactivity to *Aspergillus* virtually excludes ABPA from consideration. If the prick test is positive, serum total IgE and precipitins to *Aspergillus* should be assayed.
(See '[Evaluation](#)' above.)
- Treatment of ABPA aims to control episodes of acute inflammation and to limit progressive lung injury. Glucocorticoids are most commonly used, although there is increasing evidence of benefit from combined therapy with [itraconazole](#). (See '[Treatment](#)' above.)
- An acute flare (stage I) or recurrent exacerbation (stage III) of ABPA is treated with 0.5 to 1.0 mg/kg of [prednisone](#) daily for 14 days followed by conversion to an every other day regimen and a slow taper over three to six months. (See '[Glucocorticoids](#)' above.)
- Stage II disease (remission) and stage V disease (fibrotic lung disease) do not warrant glucocorticoid treatment. Stage IV disease (glucocorticoid-dependent asthma) is present when a patient cannot discontinue glucocorticoids without a recrudescence of asthma symptoms. (See '[Glucocorticoids](#)' above.)
- We suggest [itraconazole](#) for 16 weeks in all patients who require substantial doses of glucocorticoids, with the goal of enabling a reduction in the glucocorticoid dose. We also suggest [itraconazole](#) in patients with relapsed ABPA. The oral [itraconazole](#) regimen in adults is 200 mg three times a day for three days followed by 200 mg twice daily with food. Children should receive 5 mg/kg per day given either once a day, or if the total dose exceeds 200 mg/day, given in divided twice daily doses with food. The usual duration of

therapy is three to six months. (See ['Antifungal agents'](#) above.)

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REFERENCES

1. Greenberger, PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002; 110:685.
2. Zander, DS. Allergic bronchopulmonary aspergillosis: an overview. *Arch Pathol Lab Med* 2005; 129:924.
3. Tillie-Leblond, I, Tonnel, AB. Allergic bronchopulmonary aspergillosis. *Allergy* 2005; 60:1004.
4. Agarwal, R. Allergic bronchopulmonary aspergillosis. *Chest* 2009; 135:805.
5. Stevens, DA, Moss, RB, Kurup, VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* 2003; 37 Suppl 3:S225.
6. Riscili, BP, Wood, KL. Noninvasive pulmonary *Aspergillus* infections. *Clin Chest Med* 2009; 30:315.
7. Beaumont, F, Kauffman, HF, de Monchy, JG, et al. Volumetric aerobiological survey of conidial fungi in the North-East Netherlands. II. Comparison of aerobiological data and skin tests with mould extracts in an asthmatic population. *Allergy* 1985; 40:181.
8. Greenberger, PA, Smith, LJ, Hsu, CC, et al. Analysis of bronchoalveolar lavage in allergic bronchopulmonary aspergillosis: divergent responses of antigen-specific antibodies and total IgE. *J Allergy Clin Immunol* 1988; 82:164.
9. Kauffman, HF, Tomee, JF, van der Werf, TS, et al. Review of fungus-induced asthmatic reactions. *Am J Respir Crit Care Med* 1995; 151:2109.
10. Chauhan, B, Knutsen, AP, Hutcheson, PS, et al. T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. *J Clin Invest* 1996; 97:2324.
11. Kreindler, JL, Steele, C, Nguyen, N, et al. Vitamin D3 attenuates Th2 responses to *Aspergillus fumigatus* mounted by CD4+ T cells from cystic fibrosis patients with allergic bronchopulmonary aspergillosis. *J Clin Invest* 2010; 120:3242.
12. Gibson, PG, Wark, PA, Simpson, JL, et al. Induced sputum IL-8 gene expression, neutrophil influx and MMP-9 in allergic bronchopulmonary aspergillosis. *Eur Respir J* 2003; 21:582.
13. Agarwal, R, Aggarwal, AN, Gupta, D, Jindal, SK. *Aspergillus* hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2009; 13:936.

14. Patterson, R, Greenberger, PA, Radin, RC, Roberts, M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. *Ann Intern Med* 1982; 96:286.
15. Buckingham, SJ, Hansell, DM. Aspergillus in the lung: diverse and coincident forms. *Eur Radiol* 2003; 13:1786.
16. Reiff, DB, Wells, AU, Carr, DH, et al. CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol* 1995; 165:261.
17. Johkoh, T, Müller, NL, Akira, M, et al. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. *Radiology* 2000; 216:773.
18. Neeld, DA, Goodman, LR, Gurney, JW, et al. Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1990; 142:1200.
19. Paganin, F, Trussard, V, Seneterre, E, et al. Chest radiography and high resolution computed tomography of the lungs in asthma. *Am Rev Respir Dis* 1992; 146:1084.
20. Ward, S, Heyneman, L, Lee, MJ, et al. Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. *AJR Am J Roentgenol* 1999; 173:937.
21. Agarwal, R, Gupta, D, Aggarwal, AN, et al. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007; 132:1183.
22. Malo, JL, Longbottom, J, Mitchell, J, et al. Studies in chronic allergic bronchopulmonary aspergillosis. 3. Immunological findings. *Thorax* 1977; 32:269.
23. Greenberger, PA, Patterson, R. Diagnosis and management of allergic bronchopulmonary aspergillosis. *Ann Allergy* 1986; 56:444.
24. Vlahakis, NE, Aksamit, TR. Diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Mayo Clin Proc* 2001; 76:930.
25. Angus, RM, Davies, ML, Cowan, MD, et al. Computed tomographic scanning of the lung in patients with allergic bronchopulmonary aspergillosis and in asthmatic patients with a positive skin test to *Aspergillus fumigatus*. *Thorax* 1994; 49:586.
26. Glancy, JJ, Elder, JL, McAleer, R. Allergic bronchopulmonary fungal disease without clinical asthma. *Thorax* 1981; 36:345.
27. Berkin, KE, Vernon, DR, Kerr, JW. Lung collapse caused by allergic bronchopulmonary aspergillosis in non-asthmatic patients. *Br Med J (Clin Res Ed)* 1982; 285:552.
28. Greenberger, PA, Patterson, R. Allergic bronchopulmonary aspergillosis and the

- evaluation of the patient with asthma. *J Allergy Clin Immunol* 1988; 81:646.
29. Schwartz, HJ, Citron, KM, Chester, EH, et al. A comparison of the prevalence of sensitization to *Aspergillus* antigens among asthmatics in Cleveland and London. *J Allergy Clin Immunol* 1978; 62:9.
 30. Schwartz, HJ, Greenberger, PA. The prevalence of allergic bronchopulmonary aspergillosis in patients with asthma, determined by serologic and radiologic criteria in patients at risk. *J Lab Clin Med* 1991; 117:138.
 31. Basich, JE, Graves, TS, Baz, MN, et al. Allergic bronchopulmonary aspergillosis in corticosteroid-dependent asthmatics. *J Allergy Clin Immunol* 1981; 68:98.
 32. Eaton, T, Garrett, J, Milne, D, et al. Allergic bronchopulmonary aspergillosis in the asthma clinic. A prospective evaluation of CT in the diagnostic algorithm. *Chest* 2000; 118:66.
 33. Denning, DW, O'Driscoll, BR, Powell, G, et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009; 179:11.
 34. Bahous, J, Malo, JL, Paquin, R, et al. Allergic bronchopulmonary aspergillosis and sensitization to *Aspergillus fumigatus* in chronic bronchiectasis in adults. *Clin Allergy* 1985; 15:571.
 35. Faux, JA, Shale, DJ, Lane, DJ. Precipitins and specific IgG antibody to *Aspergillus fumigatus* in a chest unit population. *Thorax* 1992; 47:48.
 36. Simmonds, EJ, Littlewood, JM, Evans, EG. Cystic fibrosis and allergic bronchopulmonary aspergillosis. *Arch Dis Child* 1990; 65:507.
 37. Hiller, EJ. Aspergillosis. *J R Soc Med* 1992; 85 Suppl 19:33.
 38. Laufer, P, Fink, JN, Bruns, WT, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis. *J Allergy Clin Immunol* 1984; 73:44.
 39. Knutsen, AP, Hutcheson, PS, Mueller, KR, Slavin, RG. Serum immunoglobulins E and G anti-*Aspergillus fumigatus* antibody in patients with cystic fibrosis who have allergic bronchopulmonary aspergillosis. *J Lab Clin Med* 1990; 116:724.
 40. Becker, JW, Burke, W, McDonald, G, et al. Prevalence of allergic bronchopulmonary aspergillosis and atopy in adult patients with cystic fibrosis. *Chest* 1996; 109:1536.
 41. Nepomuceno, IB, Esrig, S, Moss, RB. Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole. *Chest* 1999; 115:364.
 42. Geller, DE, Kaplowitz, H, Light, MJ, Colin, AA. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. Scientific Advisory Group, Investigators, and Coordinators of the Epidemiologic Study of Cystic Fibrosis. *Chest* 1999;

116:639.

43. Fitzsimons, EJ, Aris, R, Patterson, R. Recurrence of allergic bronchopulmonary aspergillosis in the posttransplant lungs of a cystic fibrosis patient. *Chest* 1997; 112:281.
44. CAMPBELL, MJ, CLAYTON, YM. BRONCHOPULMONARY ASPERGILLOSIS. A CORRELATION OF THE CLINICAL AND LABORATORY FINDINGS IN 272 PATIENTS INVESTIGATED FOR BRONCHOPULMONARY ASPERGILLOSIS. *Am Rev Respir Dis* 1964; 89:186.
45. McCarthy, DS, Pepys, J. Allergic broncho-pulmonary aspergillosis. *Clinical immunology*. 2. Skin, nasal and bronchial tests. *Clin Allergy* 1971; 1:415.
46. Rosenberg, M, Patterson, R, Mintzer, R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; 86:405.
47. Chapman, BJ, Capewell, S, Gibson, R, et al. Pulmonary eosinophilia with and without allergic bronchopulmonary aspergillosis. *Thorax* 1989; 44:919.
48. Walsh, TJ, Anaissie, EJ, Denning, DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46:327.
49. Breslin, AB, Jenkins, CR. Experience with allergic bronchopulmonary aspergillosis: some unusual features. *Clin Allergy* 1984; 14:21.
50. Golbert, TM, Patterson, R. Pulmonary allergic aspergillosis. *Ann Intern Med* 1970; 72:395.
51. Ricketti, AJ, Greenberger, PA, Patterson, R. Serum IgE as an important aid in management of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 1984; 74:68.
52. Agarwal, R, Gupta, D, Aggarwal, AN, et al. Clinical significance of decline in serum IgE levels in allergic bronchopulmonary aspergillosis. *Respir Med* 2010; 104:204.
53. Marchant, JL, Warner, JO, Bush, A. Rise in total IgE as an indicator of allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 1994; 49:1002.
54. Stevens, DA, Schwartz, HJ, Lee, JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000; 342:756.
55. Wark, PA, Gibson, PG, Wilson, AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst Rev* 2004; :CD001108.
56. Wark, PA, Hensley, MJ, Saltos, N, et al. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. *J Allergy Clin Immunol* 2003; 111:952.
57. Pasqualotto, AC, Powell, G, Niven, R, Denning, DW. The effects of antifungal

therapy on severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis. *Respirology* 2009; 14:1121.

58. Salez, F, Brichet, A, Desurmont, S, et al. Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. *Chest* 1999; 116:1665.
59. Lebrun-Vignes, B, Archer, VC, Diquet, B, et al. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; 51:443.
60. Varis, T, Kaukonen, KM, Kivistö, KT, Neuvonen, PJ. Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; 64:363.
61. Bolland, MJ, Bagg, W, Thomas, MG, et al. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. *Ann Pharmacother* 2004; 38:46.
62. Woods, DR, Arun, CS, Corris, PA, Perros, P. Cushing's syndrome without excess cortisol. *BMJ* 2006; 332:469.
63. Parmar, JS, Howell, T, Kelly, J, Bilton, D. Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002; 57:749.
64. Skov, M, Main, KM, Sillesen, IB, et al. Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *Eur Respir J* 2002; 20:127.
65. Wong, J, Black, P. Acute adrenal insufficiency associated with high dose inhaled steroids. *BMJ* 1992; 304:1415.
66. Erwin, GE, Fitzgerald, JE. Case report: allergic bronchopulmonary aspergillosis and allergic fungal sinusitis successfully treated with voriconazole. *J Asthma* 2007; 44:891.
67. Glackin, L, Leen, G, Elnazir, B, Greally, P. Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis. *Ir Med J* 2009; 102:29.
68. Laoudi, Y, Paolini, JB, Grimfed, A, Just, J. Nebulised corticosteroid and amphotericin B: an alternative treatment for ABPA? *Eur Respir J* 2008; 31:908.
69. Howard, SJ, Pasqualotto, AC, Denning, DW. Azole resistance in allergic bronchopulmonary aspergillosis and *Aspergillus* bronchitis. *Clin Microbiol Infect* 2010; [Epub ahead of print].
70. Zirbes, JM, Milla, CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol* 2008; 43:607.
71. van der Ent, CK, Hoekstra, H, Rijkers, GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax*

2007; 62:276.

72. Kanu, A, Patel, K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). *Pediatr Pulmonol* 2008; 43:1249.
73. Lebecque, P, Leonard, A, Pilette, C. Omalizumab for treatment of ABPA exacerbations in CF patients. *Pediatr Pulmonol* 2009; 44:516.
74. Brinkmann, F, Schwerk, N, Hansen, G, Ballmann, M. Steroid dependency despite omalizumab treatment of ABPA in cystic fibrosis. *Allergy* 2010; 65:134.

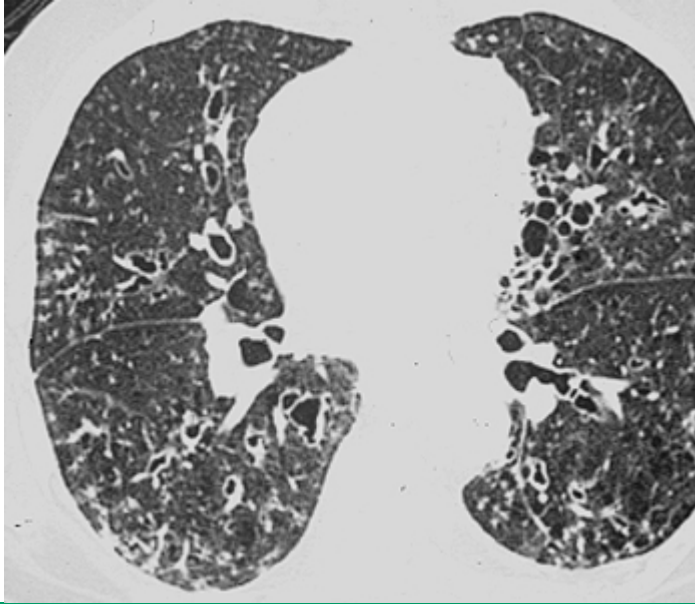
GRAPHICS

Stages of allergic bronchopulmonary aspergillosis

Classification	Description	Radiographic infiltrates	Total serum IgE
I	Acute	Upper lobes or middle lobe	Markedly elevated
II	Remission	No infiltrate; off prednisone >6 mo	Elevated or normal
III	Exacerbation	Upper lobes or middle lobe	Markedly elevated
IV	Corticosteroid-dependent asthma	Infiltrates absent or only intermittent	Elevated or normal
V	End stage	Fibrotic, bullous or cavitary lesions	May be normal

Data from: Patterson, R, Greenberger, PA, Radin, RC, Roberts, M. Allergic Bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med 1982;96 286.

Central bronchiectasis



Central bronchiectasis in a patient with allergic bronchopulmonary aspergillosis. Multiple dilated third and fourth generation bronchi are seen. Smaller peripheral bronchi filled with mucus account for the branching linear opacities in the distal lung parenchyma.

Courtesy of Paul Stark, MD.

